ENHANCED RECTAL ABSORPTION OF LINCOMYCIN

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The oral administration of antibiotics, particularly on prolonged dosage, can deleteriously influence gut flora, resulting in gastrointestinal and metabolic disturbances(George 1977). An appropriate rectal dosage form may provide a convenient means of circumventing these problems whilst retaining therapeutic efficacy. In this report we describe our findings with lincomycin following its rectal administration to rabbits and healthy volunteers. Preliminary studies indicated that lincomycin is poorly absorbed rectally. We therefore investigated two methods for enhancing its absorption; selective derivatisation, and the incorporation of non-ionic surface active agents (surfactants) into the suppository formulation. Initial screening and rectal irritation studies were performed in rabbits and the most promising formulation tested in volunteers.

Unfasted New Zealand White rabbits, 3.5-4.0 kg body weight and male volunteers aged 20-40 years were used in these studies. The suppository formulations were prepared by simple incorporation of the antibiotic, and surfactant when appropriate, into the molten suppository base at 40°C. Of several commercially available suppository bases screened, Base BD (Henkel and Cie) was selected as the most appropriate. The two surfactants used, Brij 58 (polyoxyethylene-20-cetyl ether; Honeywill-Atlas) and Texafor B1 (polyoxyethylene-16-lauryl ether; Glover Chemicals) were selected from a series of non-ionic and cationic surfactants on the basis of their efficacy and low potential for causing rectal irritation, and were incorporated into the suppositories at a concentration of 5% w/w.

In the rabbit studies (n = 3 or 6), the dose of lincomycin HCl (L) and four of its esters [lincomycin-2-propionate HCl (L2P), 3-propionate HCl (L3P), 2-hexanoate HCl (L2H) and 3-hexanoate HCl (L3H)] was equivalent to 92 mg lincomycin free base in a 500 mg suppository. In the human study (single blind cross over), 2 g suppositories containing L equivalent to a dose of 500 mg lincomycin free base were used. Blood samples were taken at 0 h and at various time points up to 8 h, after administration of the suppositories. A multiple dose regimen was adopted, suppositories being administered at 0, 8, 16 and 24 h, to assess any cumulative effects. Urine samples were also collected.

In the ester studies in rabbits, when no surfactant was incorporated into the suppository, the order of activity in terms of peak plasma lincomycin level and area under the curve was L3H = L2P > L = L2H > L3P, with peak drug levels ranging from 3-13 µg/ml at 15-30 min. In a study with L3H, inclusion of the surfactants resulted in a lowering of the peak drug level by about 40% whereas incorporation of the surfactants into L suppositories promoted a 7 to 8-fold increase in peak lincomycin level (20-24 µg/ml). In the human study, inclusion of Brij 58 in the L suppository resulted in a 2-fold increase in peak drug level (7-9 µg/ml vs. 3-4 µg/ml), a 50% increase in area under the curve and a 2-fold increase in urinary elimination (13% vs. 7% of the administered dose).

In conclusion, these preliminary studies have indicated the value of selective derivatisation and surfactants in enhancing the rectal absorption of lincomycin.

George W.L., Sutter V.L. and Finegold S.M., J. Infect. Dis. (1977) 136 822-828.

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